Journal of Molecular Structure 1035 (2013) 358–362

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Spatial structure of felodipine dissolved in DMSO by 1D NOE and 2D NOESY NMR spectroscopy

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HIGHLIGHTS

- Internuclear distances in felodipine were obtained by analysis of 1D and 2D NOE data.
- Obtained effective distances were compared with quantum-chemical calculations.
- Fractions of different conformers of felodipine dissolved in DMSO were estimated.

ARTICLE INFO

Article history:
Received 23 October 2012
Received in revised form 8 November 2012
Accepted 19 November 2012
Available online 27 November 2012

Keywords:
Conformational analysis
Nuclear magnetic resonance
NOE
Jump model

ABSTRACT

Small organic molecules in dissolved state exist as an ensemble of conformers. In this work conformation of felodipine in dimethyl sulphoxide was studied and dominant stable conformers were determined. Effective interatomic distances were obtained by means of NOE spectroscopy. Fractions of different conformers were estimated by comparing effective distances and those obtained from quantum-chemical calculation [8]; averaging of distances was made following the N-site jump model.

1. Introduction

Accurate determination of interproton distances in relatively small, flexible molecules by 1D and 2D NOE NMR spectroscopy is the subject of increasing interest in recent years [1–3]. Results of such investigations can be applied to establishing conformational details for biologically active molecules in solutions. It is well known that polymorphism of drug compounds affects the biological activity and plays an important role in the production of pharmaceuticals. In turn, the properties of polymorphs are due to molecular structure of compounds and their ability to exist in different conformational forms in the solvent from which recrystallization is performed. Therefore, search for new polymorphic forms of drugs is closely associated with the study of conformational states of biologically active molecules in solutions.

Felodipine (ethylmethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate) is widely used as antihypertensive and antianginal drug [4]. The possible existence of different polymorphic forms connected with conformations of the phenyl ring was predicted in [5]. Commercial felodipine has the melting point of 144 °C and is a racemic mixture of enantiomers [6]. Some researches point to existence of three or more crystal structures [5,7].

Conformational flexibility of felodipine is determined by two dihedral angles: (C3—C4—C1′—C2′), which defines the rotation of 2,4-dichlorophenyl group around C1′—C4 bond, and (C3a—O—C3b—C3c), related with the rotation of ethyl group around O—3b bond (Fig. 1). Teberekidis and Sigalas in 2007 published the result of a theoretical study of felodipine using a hybrid density functional method B3LYP [8]. They revealed six conformers with very close energies (within 4.2 kJ/mol), starting from number 1 (the global minimum) up to number 6 (with the maximal energy). It is important for the purposes of further discussion, that in the conformers 1, 2, and 5 chlorine atoms point to the same direction as NH1 proton, whereas in the conformers 3, 4, and 6 the dichlorophenyl ring is turned by 180° and chlorine atoms are closer to the H4 proton (Figs. 2 and 3).

Obvious progress was made recently in determining interproton distances from NOE data. Butts et al. [9] gave a convincing example

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http://dx.doi.org/10.1016/j.molstruc.2012.11.040